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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.
09/335,689	06/18/99	TOUSIGNANT J	6969.0028

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EXAMINER	
SCHNIZER,R	
ART UNIT	**PAPER NUMBER**
1632	10

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Please find below and/or attached an Office communication concerning this application or proceeding.

Commissioner of Patents and Trademarks

Office Action Summary	Application No. 09/335,689	Applicant(s) TOUSIGNANT ET AL.	
	Examiner Richard Schnizer	Art Unit 1632	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136 (a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *23 October 2000* .

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-30* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-30* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claims _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are objected to by the Examiner.

11)☐ The proposed drawing correction filed on _____ is: a)☐ approved b)☐ disapproved.

12)☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. § 119

13)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____ .

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

14)☐ Acknowledgement is made of a claim for domestic priority under 35 U.S.C. & 119(e).

Attachment(s)

15) ☐ Notice of References Cited (PTO-892)
16) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
17) ☐ Information Disclosure Statement(s) (PTO-1449) Paper No(s) _____ .
18) ☐ Interview Summary (PTO-413) Paper No(s). _____ .
19) ☐ Notice of Informal Patent Application (PTO-152)
20) ☐ Other: .

DETAILED ACTION

Election/Restriction

An amendment was received ands entered as Paper No. 9 on 10/23/00. Claims 1-30 remain pending in the application and are under consideration in this office action.

Rejections Withdrawn

The rejection of claims 1-30 under 35 U.S.C. 112, first paragraph is withdrawn in view of Applicant's amendment which eliminated the limitation requiring a variation in size distribution of less than 20% relative to the average size of a complex in a group of micellar complexes. As a result of this amendment, this limitation is no longer considered to be representative of the scope of claims 1-30.

The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

Claims 1-16 and 25-30 stand rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention, for the reasons of record in paper No. 8, and for the new grounds set forth below.

Claims 1-16 and 25-30 are indefinite because it is unclear what is intended by the phrase "substantially homogenous size distribution". In this context, the term "substantially" is a relative term which modifies the term "homogenous". The term "substantially" is not defined by the claim, the specification does not provide a standard for ascertaining the requisite degree, and the term does not specify an art-recognized quantity. Specifically, the term "substantially" renders indefinite the degree of homogeneity required by the claims. Applicant argues that the specification defines the phrase "substantially homogenous size distribution" as meaning a narrower size distribution than "lipid complexes prepared by traditional means". This is unpersuasive because it is not clear to which lipid complexes, and to which traditional means, Applicant refers. This definition could encompass all lipid complexes prepared by all traditional means. Alternatively it may encompass only some complexes prepared by only certain traditional means. Furthermore it is unclear which means are traditional. Does this refer to any means known in the prior art, or only the most widely practiced? How widely must a technique be practiced in order to qualify as traditional? The claims are indefinite because the meaning of "substantially homogenous" cannot be determined from the specification.

Claims 5 and 27 are incomplete because they require a size distribution of less than 20%, but fail to recite of what quantity or quality 20% is a fraction. One is left to ask, twenty percent of what?

Claim 16 is indefinite because it requires a variation in size distribution of less than 20%, but fails to provide any standard from which to calculate 20% variation.

Claims 25-30 recite the phrase "a substantially homogenous size distribution". This phrase is indefinite because the specification does not provide a limiting definition. At page 17, an example is given wherein the size distribution of a traditional lipid complex may vary by greater than 50%, whereas that of the instant invention may vary by only about 20%. Is "about 20%" variation intended to be the definition of "substantially homogenous"? What is encompassed by "about 20%"? Would a size distribution varying by 25-30% infringe on the invention? The claims are indefinite because the meaning of "substantially homogenous" cannot be determined from the specification.

Claim Rejections - 35 USC § 102

The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless --
>
> (b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.
>
> (e) the invention was described in a patent granted on an application for patent by another filed in the United States before the invention thereof by the applicant for patent, or on an international application by another who has fulfilled the requirements of paragraphs (1), (2), and (4) of section 371(c) of this title before the invention thereof by the applicant for patent.

Claims 1-3, 5, 6, 9-11, 13, 14, 16-19, 21, 22, 24-29 stand rejected under 35 U.S.C. 102(b) as being anticipated by Harris et al (US Patent 5,719,131, issued 2/17/98), for the reasons of record in Paper No. 8.

Harris teaches a method of making micellar complexes comprising a cationic lipid, a PEG derivatized colipid, and DNA. See column 26, lines 4-11 and 32-36; column 37, lines 24-53; and column 45, line 56 to column 46, line 5. Applicant argues that Harris fails to teach micellar complexes of a substantially homogenous size distribution. However, because the specification fails to adequately define the phrase "substantially homogenous size distribution" for the reasons discussed above, a composition of micellar complexes made by the method of Harris is considered to have a substantially homogenous size distribution, absent evidence to the contrary. Claim 5 is included in this rejection because, as amended, its limitation regarding size distribution is indefinite. Thus, absent evidence to the contrary, Harris also anticipates claim 5. Claims 6, 13, and 21 are included in this rejection because these methods and compositions do not appear to be distinguishable from the teachings of Harris. Specifically, the claims are drawn to micellar compositions coated with a hydrophobic species. The specification teaches that the compositions are made by adding the hydrophobic species to the micellar compositions. This would seem to be inherent in the method of making the initial micellar compositions. The addition of lipid micelles to DNA would result in condensation of the DNA around cationic lipids, and any uncomplexed lipids would be available to coat the DNA. In light of the description of the invention in the specification at page 20, it would seem that hydrophobic coating of the micelles would be unavoidable. Applicant argues that one of skill in the art would know how much cationic amphiphile to use, based on the amount of biologically active molecules (DNA) present, so that there would be a statistically insignificant amount of cationic amphiphiles left over to coat the

complexes. This is unpersuasive because such a ratio of micellar complex components is not required by the claims, and because Applicant has failed to show that such ratios are employed in the method of the cited prior art.

It is also noted that Applicant's arguments with respect to the meaning of the phrase "substantially homogenous size distribution" do not apply to claims 17-19, 21, 22, and 24 which do not recite that limitation.

Thus Harris anticipates the claims.

Claims 1-3, 6-14, 16-19, and 21-30 rejected under 35 U.S.C. 102(e) as being anticipated by Unger (US Patent 6,028,066, filed 5/2/97).

Unger teaches a method of making micellar complexes by combining micellar lipids with a bioactive agent which may be DNA. See column 79, lines 20-37; column 2, lines 59-65; column 6, lines 10-24, especially lines 22 and 23; and column 6, lines 55-57. The micellar lipids may comprise PEG-modified lipids. See column 22, line 19 to column 24, line 1, especially column 22, lines 60-67. The complexes may comprise targeting moieties, and may include peptides with RGD sequences. See column 6, lines 45-51; and column 19, lines 54-58. Unger also teaches delivery of the complexes to mammalian airway cells. See column 84, lines 24-28.

Applicant argues that Harris fails to teach micellar complexes of a substantially homogenous size distribution. However, because the specification fails to adequately define the phrase "substantially homogenous size distribution" for the reasons discussed above, a composition of

micellar complexes made by the method of Unger is considered to have a substantially homogenous size distribution, absent evidence to the contrary. Claim 5 is included in this rejection because, as amended, the limitation regarding size distribution is indefinite. Absent evidence to the contrary, Unger also anticipates claim 5. Claims 6, 13, and 21 are included in this rejection because these methods and compositions do not appear to be distinguishable from the teachings of Unger. Specifically, the claims are drawn to micellar compositions coated with a hydrophobic species. The specification teaches that the compositions are made by adding the hydrophobic species to the micellar compositions. This would seem to be inherent in the method of making the initial micellar compositions. The addition of lipid micelles to DNA would result in condensation of the DNA around cationic lipids, and any uncomplexed lipids would be available to coat the DNA. In light of the description of the invention in the specification at page 20, it would seem that hydrophobic coating of the micelles would be unavoidable. Applicant argues that one of skill in the art would know how much cationic amphiphile to use, based on the amount of biologically active molecules (DNA) present, so that there would be a statistically insignificant amount of cationic amphiphiles left over to coat the complexes. This is unpersuasive because such a ratio of micellar complex components is not required by the claims, and because Applicant has failed to show that such ratios are employed in the method of the cited prior art.

It is also noted that Applicant's arguments with respect to the meaning of the phrase "substantially homogenous size distribution" do not apply to claims 17-19 and 21-25 which do not recite that limitation.

Thus Unger anticipates the claims.

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

Claims 1, 4, 15, and 20 are rejected under 35 U.S.C. 103(a) as being unpatentable over Harris et al (US Patent 5,719,131, issued 2/17/98).

Harris teaches a method of making micellar complexes wherein 64 different cationic lipid suspensions were combined with equal volumes of 64 different DNA solutions. Briefly, eight 165 microliter lipid suspensions of different concentrations were deposited into 8 different wells of a microtiter plate. Sixty four different lipid suspensions were then made by seven 2-fold dilutions of each of the initial eight suspensions. This results in 64 suspensions of 165 microliters. A similar operation was carried out for the DNA solutions, and the contents of the microtiter plates were combined pairwise, resulting in 64 lipid-DNA suspensions. Among the mass ratios of lipid to DNA which were encompassed were 0.7:1, 1.4:1, 5.6:1, and 11.2:1. Although Harris does not teach the combination of lipid and DNA in an 8:1 vol:vol ratio, this volume ratio would have been obvious in view of the fact that Harris could just as easily have used equimolar solutions of both lipids and DNA and added the appropriate volumes of each to arrive at the range of mass

concentrations taught by Harris. One would have been motivated in this instance to use a ratio of 8:1 vol:vol to achieve a lipid:DNA mass ratio of 8:1. One would have been motivated to achieve this ratio because the concentration of each of these components is a result-effective variable. That is, the results of a technique using the composition are effected by concentrations of each of these variables, and one of ordinary skill would be motivated to optimize the concentrations of each variable. Generally, differences in concentration will not support the patentability of subject matter encompassed by the prior art unless there is evidence indicating that this concentration is critical. See MPEP 2144.05(b). In this case, the specification and claims disclose that ratios of 1:1 and 8:1 will yield the claimed compositions. See Figures 3 and 4, and claims 4, 15, and 20. Thus the claimed ratio of 8:1 does not appear to be absolutely required for the function of the invention. Harris teaches ratios covering the range of ratios disclosed as functional by Applicant. "[W]here the general conditions of a claim are disclosed in the prior art, it is not inventive to discover the optimum or workable ranges by routine experimentation." *In re 0Aller*, 220 F.2d 454 105 USPQ 233, 235 (CCPA 1955).

Thus the invention was *prima facie* obvious.

Applicant argues that one of skill in the art would know how much cationic amphiphile to use, based on the amount of biologically active molecules (DNA) present, so that there would be a statistically insignificant amount of cationic amphiphiles left over to coat the complexes. This is unpersuasive because such a ratio of micellar complex components is not required by the claims,

and because Applicant has failed to show that such ratios are employed in the method of the cited prior art.

Conclusion

No claim is allowed.

Applicant's amendment necessitated the new ground(s) of rejection presented in this Office action. Accordingly, **THIS ACTION IS MADE FINAL**. See MPEP § 706.07(a). Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the date of this final action.

Any inquiry concerning this communication or earlier communications from the examiner(s) should be directed to Richard Schnizer, whose telephone number is 703-306-5441. The examiner can normally be reached on Mondays and Thursdays between the hours of 6:20 AM and 3:50 PM, and on Tuesdays, Wednesdays and Fridays between the hours of 7:00 AM and

4:30 PM (Eastern time). The examiner is off every other Friday, but is usually in the office anyway.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Karen Hauda, can be reached at 703-305-6608. The FAX phone numbers for art unit 1632 are 703-308-4242 and 703-305-3014.

Inquiries of a general nature or relating to the status of the application should be directed to the group receptionist whose telephone number is 703-308-0196.

Questions regarding formal matters may be directed to the Patent Analyst, Patsy Zimmerman, whose telephone number is 703-305-2758.

Richard Schnizer, Ph. D.

SCOTT D. PRIEBE, PH.D
PRIMARY EXAMINER